Effect of Mifepristone for Symptomatic Leiomyomata on Quality of Life and Uterine Size

A Randomized Controlled Trial

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OBJECTIVE: To assess the effect of low-dose mifepristone on quality of life, pain, bleeding, and uterine size among women with symptomatic leiomyomata.

METHODS: Forty-two women with symptomatic uterine leiomyomata and uterine volume of 160 mL or more were randomized to mifepristone, 5 mg daily, or placebo for 26 weeks. Quality of life (Uterine Fibroid Symptoms Quality of Life Questionnaire and Medical Outcomes Study 36-Item Short Form survey) and uterine and leiomyoma size (ultrasonography) were assessed at baseline, and at 1 month, 3 months, and 6 months of treatment. Bleeding (daily logs and pictorial charts) and pain (McGill Pain Questionnaire) were assessed monthly. Endometrial pathology was assessed at baseline and 6 months.

RESULTS: Forty-two women were randomized; 37 women completed all 6 months. Women randomized to mifepristone showed an improvement in leiomyoma-specific quality of life. Forty-one percent became amenorrheic, rates of anemia improved, and adjusted uterine size was reduced by 47%. Compared with the placebo group, improvements in these outcomes in the treatment group were significantly greater ($P<.05$ to .001). There were no significant differences in adverse effects between the groups. No endometrial hyperplasia was noted in any participant.

CONCLUSION: Low-dose mifepristone improves leiomyoma-specific quality of life and reduces leiomyoma size among women with symptomatic leiomyomata.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00133705

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LEVEL OF EVIDENCE: I

Roughly half of all women aged 35–49 years have uterine leiomyomata,[1] and nearly half of these have heavy bleeding,[2] often causing iron-deficiency anemia. Seven percent of women with uterine leiomyomata report moderate-to-severe pain.[3] More than 1.2 million women were hospitalized in the United States with a primary diagnosis of leiomyomata between 1998 and 2002, resulting in more than one million hysterectomies and 150,000 myomectomies.[4] Absence of an approved medical treatment contributes to high rates of surgical treatment for leiomyomata.

Observational data suggest that treatment with mifepristone, an antiprogestin, is associated with reduction in uterine and leiomyoma size, pain, and bleeding.[5] Early studies of women with leiomyomata suggest comparable improvement in leiomyoma symptoms and reductions in leiomyoma size with mifepristone doses of 50 mg, 25 mg, and 10 mg.[5] More recent data show that mifepristone 5 mg yields improvement in symptoms and reductions in size that is comparable with mifepristone 10 mg.[6] However, the benefits of mifepristone have not been confirmed through randomized, double-blinded, placebo-controlled trials or through use of validated leiomyoma-specific quality-of-life measures.

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PARTICIPANTS AND METHODS

The primary aim of the study was to test the hypothesis that mifepristone 5 mg daily for 6 months improves leiomyoma-specific quality of life among women with symptomatic leiomyomata. Secondary aims were to assess whether the drug improves global quality of life, bleeding, uterine and leiomyoma size, and pain without inducing significant endometrial pathology.

Women were eligible for inclusion in the trial if they were 18 years of age or older, were premenopausal, reported at least moderately severe leiomyoma-related symptoms (more than 39 on the Uterine Fibroid Symptom Quality of Life Symptom Severity Subscale),[7] had a total uterine volume by vaginal and abdominal ultrasound 160 mL or more and at least one leiomyoma that was 2.5 cm or larger, had not used short-acting hormones in the past 3 months, and had not used gonadotropin-releasing hormone analogues or other long-acting hormonal medications in the past 6 months. Women were excluded if they were pregnant or intended to become pregnant during the next 6 months or had major medical morbidity or severe anemia, active mental illness, elevated liver enzymes, or substance abuse. Participants agreed to use barrier contraception and not to use hormonal or surgical treatments for leiomyomata during the course of the trial. Analgesic use was permitted.

Women were recruited between March 3, 2004, and March 30, 2005, through local media and contacts with community physicians. Participant flow through the study is illustrated in Figure 1. Women with symptoms of leiomyoma disease who met preliminary eligibility criteria were encouraged to call a dedicated number to speak with a research assistant for information. A total of 434 women called; of those, 137 (32%) were not interested in participating,

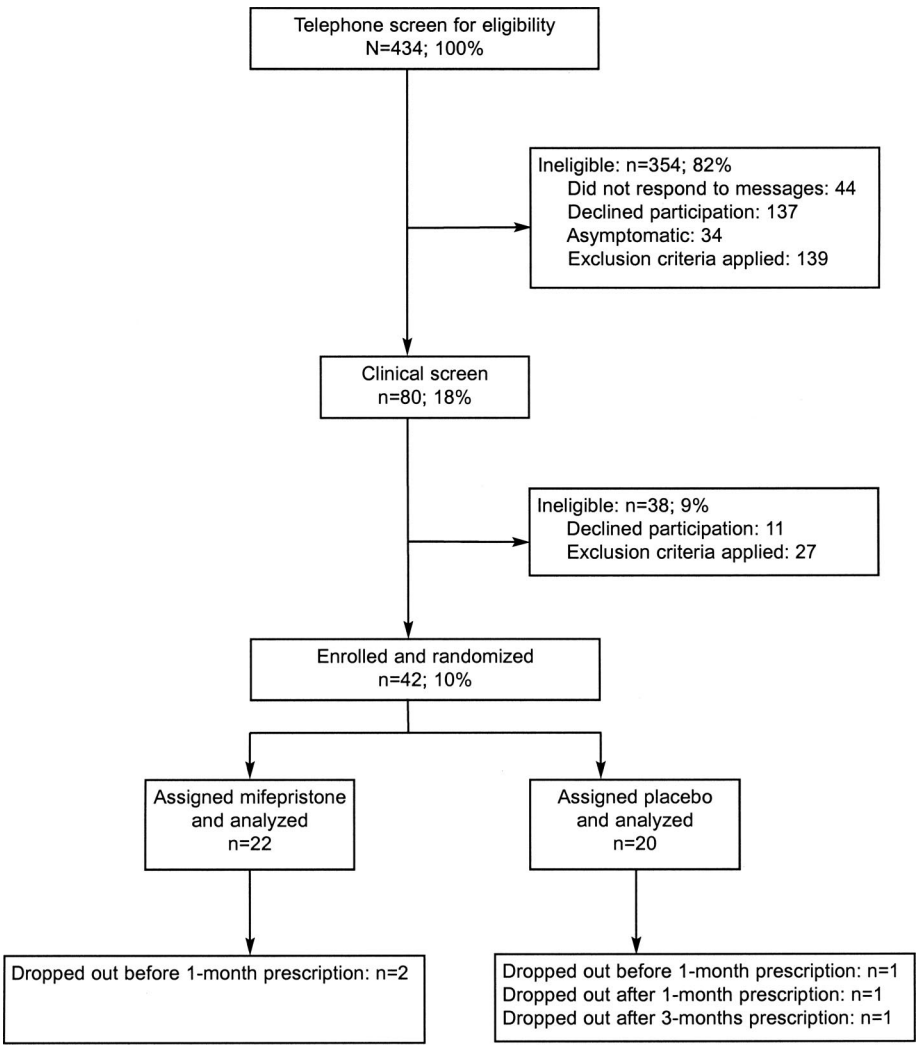

Fig. 1. Participant flow through the study.

Fiscella. Effect of Mifepristone on Quality of Life. Obstet Gynecol 2006.

44 (10%) left messages but did not respond to repeated call-backs, 34 (8%) described symptoms that were too mild to be included, and 139 (32%) were symptomatic but were ineligible for other reasons, including current use of hormonal contraceptives, desire to become pregnant, significant comorbidities, or a current ultrasonogram that showed few or no leiomyomata.

The remaining 80 (18%) women who called passed the telephone prescreen and agreed to visit the investigators to provide informed consent, for an intake interview conducted at the research facility, and for baseline physical and biochemical examination performed at the hospital. These included physical examination, ultrasound examination, blood tests, and endometrial biopsy. Of the 80 women who were consented and scheduled intake exams, 11 (14%) declined further participation, 27 (34%) were excluded for clinical reasons, 3 (4%) completed the intake measures and were randomized (two to treatment and one to placebo) but then declined to participate, and 39 (49%) began the trial and participated for at least one month. Trial participants were randomly assigned to take either 5 mg mifepristone daily or an identical-appearing placebo. All 42 women who were randomized were included in the analysis, including the three who provided only baseline measures and two more who withdrew later.

All women provided written and verbal informed consent at each stage. The study was approved by the University of Rochester Institutional Review Board and registered through ClinicalTrials.gov, number NCT00133705. Women were paid for each study visit to defray their expenses.

The study pharmacist prepared mifepristone 5 mg and placebo in capsules that were identical in appearance and weight. Using random numbers generated with SAS 9 (SAS Institute Inc, Cary, NC), women were randomly assigned in blocks of four, stratified by Uterine Fibroid Symptom Quality of Life symptom severity (greater than 64 versus 63 or less) to mifepristone 5 mg or placebo taken once daily. Study assignments were placed in opaque sealed envelopes that were opened by the study pharmacist once the participant was fully qualified. None of the study personnel, with the exception of the pharmacist, were aware of treatment assignments. Protocol adherence was determined from monthly logs and counts of returned pills.

Participants were permitted to use analgesics, including nonsteroidal anti-inflammatory agents, during the study but were asked to record the type of analgesic and amount taken in monthly logs. Other treatments for leiomyomata, including hormonal treatments, were not permitted.

Outcomes were assessed using validated measures. The primary outcome was mean change in leiomyoma-specific overall quality of life (Uterine Fibroid Symptom Quality of Life[7]) scale 1–100, with higher scores indicating better quality of life. A sample question from this scale is this: "During the past month, how distressed were you by: heavy bleeding during your menstrual period; feeling tightness or pressure in your pelvic area, or feeling fatigued?" The Uterine Fibroid Symptom Quality of Life includes secondary scales to measure perceived impact of leiomyomata on activities of daily living, general concern and worry, energy and mood, sense of self-control, self-consciousness, and sexual functioning. Secondary measures included global health status (the Medical Outcomes 36-item Short Form [SF-36] survey[8]) and global pain (McGill Pain Questionnaire).[9] Each of these questionnaires was administered at baseline, 1 month, 3 months, and 6 months, except the McGill Pain Questionnaire, which was assessed monthly. Bleeding was assessed by using daily menstrual logs and pictorial bleeding charts.[10] A monthly blood loss index was calculated from menstrual history by assigning values 1–4 to each day of spotting, indicating light, moderate, and heavy flow, respectively, and then summing the results. Monthly assessments of the presence and intensity of likely leiomyoma symptoms (including pelvic pain, pelvic pressure, bladder pressure, urinary frequency, low back pain, rectal pain, and pain with intercourse) and drug adverse effects (including hot flushes, headache, nausea, vomiting, mood swings, diarrhea, decreased libido, weakness, fatigue, and nervousness) were performed with a standardized instrument consisting of 5-point Likert scale items. Uterine volume and leiomyoma size and number were assessed by vaginal and/or abdominal ultrasonogram (depending on leiomyoma size) at baseline, 1 month, 3 months, and 6 months. The uterus was measured in three planes and a total volume calculated. The five largest leiomyomata were identified, a volume calculated for each of the leiomyomata, and the results summed. Baseline uterine volume was subtracted from each subsequently measured uterine volume, and volume changes were analyzed. Safety monitoring included monthly pregnancy testing, hemoglobin levels, and liver function testing at baseline, 1, 3, and 6 months. All participants underwent endometrial biopsy at baseline and 6-month follow-up (or when possible, upon termination from study).

The planned sample size was 70. Based upon previous reports,[7] we estimated that the standard deviation of the observed Uterine Fibroid Symptom Quality of Life scores would be approximately 25

points, suggesting that 70 participants would yield 80% power to detect a difference of 17 points in mean Uterine Fibroid Symptom Quality of Life total score between two treatment groups with significance level .05. Seventeen points on the Uterine Fibroid Symptom Quality of Life scale is roughly equivalent to the difference between severe and moderate symptoms. A post hoc power analysis using the observed Uterine Fibroid Symptom Quality of Life standard deviation of 27 points and the 37 women who completed all 6 months of the trial revealed that our final analysis was powered to detect a 25-point difference in mean Uterine Fibroid Symptom Quality of Life scores.

Differences in Uterine Fibroid Symptom Quality of Life scores, ultrasound measures, bleeding, pain, and other longitudinal measures were assessed by using individual growth curve models. Independent variables included in each model were treatment group, month, and an interaction term for treatment group and month (used to assess whether the treatment effect of mifepristone changed with time). Unless otherwise noted, approximate *t* tests were obtained by using regression contrasts to test custom hypotheses of between-group and within-group differences in outcomes. Statistical analyses were performed with the SAS System for mixed models (SAS Institute Inc, Cary, NC). All women who were randomized (42) were included in the analysis. There were very few missing data. Quality of life measures, ultrasonograms, and logs were collected from all women.

RESULTS

Participant flow, including screening, enrollment, and dropouts, is shown in Figure 1. Despite intensive efforts, only 42 women met all eligibility criteria and consented during the allotted enrollment period. Twenty-two were randomized to treatment and 20 to placebo. The two groups were well matched for baseline characteristics with the exception of body mass index (body weight [kg]/height [m]^2) and baseline uterine volume (Table 1).

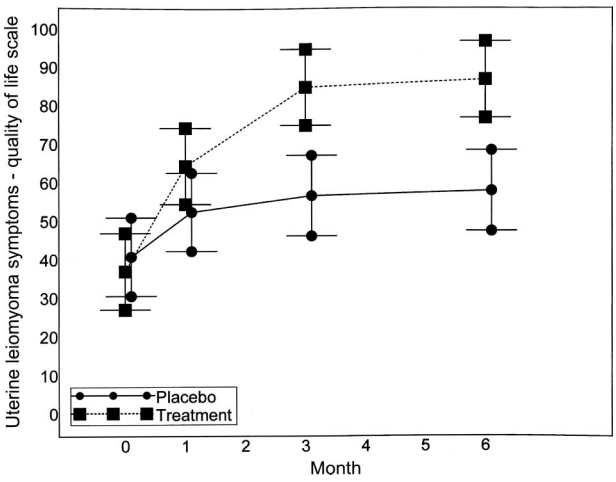

Fig. 2. Change in uterine leiomyoma-specific quality of life among mifepristone and placebo groups. Uterine leiomyoma-specific quality of life was measured using the total score on the Uterine Leiomyoma Symptom Quality of Life scale. Bars represent 95% confidence intervals surrounding change in the score at each time point.
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Three women, two from the treatment group and one from the placebo, dropped out immediately after randomization before any follow-up measures could be obtained (Fig. 1). Three women dropped out during the course of the study. None reported leaving due to adverse effects. Adherence was high among continuing participants. Women in both the treatment and control groups reported missing only three doses per month.

Mean Uterine Fibroid Symptoms Quality of Life leiomyoma-specific quality of life measures were similar between groups at baseline. Significant

Table 1. Characteristics of Participants Randomized

	Treatment (n=22)			Placebo (n=20)		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Age (y)	44.8 (6.2)	43	29–54	43.2 (4.7)	44	31–50
Body mass index (kg/m^2)	31.7 (8.7)	32	21–52	27.2 (5.6)	26	20–39
Education (y)	14.6 (2.3)	14	12–19	15.1 (2.5)	15	11–22
Gravidity	2.6 (2.1)	3	0–7	2.4 (2.1)	2	0–7
Parity	1.8 (1.6)	2	0–6	1.6 (1.5)	2	0–5
Uterine volume (mL)	719 (663)	506	173–2,488	449 (236)	392	210–1,103
African American [n (%)]	11 (50)	–	–	11 (55)	–	–

SD, standard deviation.

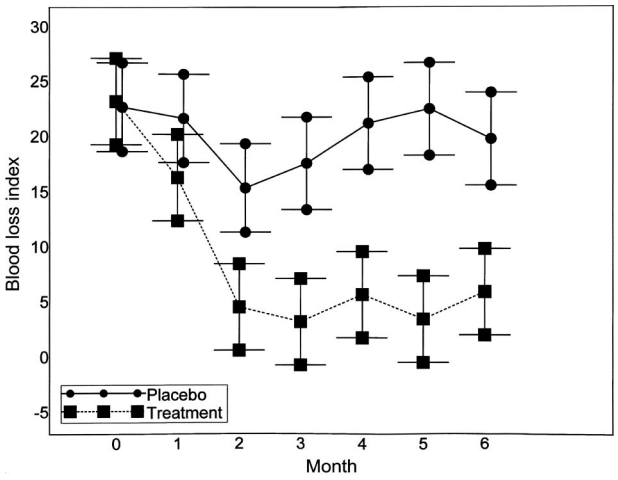

Fig. 3. Change in bleeding patterns among mifepristone and placebo groups. Bleeding patterns were measured by bleeding scores derived from product of bleeding intensity from pictorial blood chart and days of bleeding. Bars refer to 95% confidence intervals surrounding changes in bleeding patterns at each time point.

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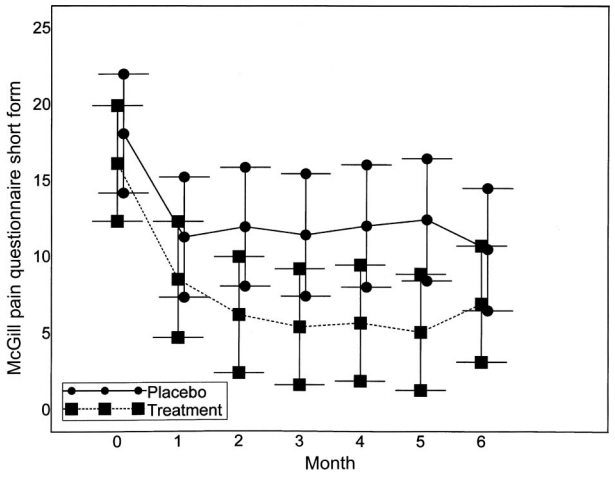

Fig. 4. Change in pain among mifepristone and placebo groups. Pain was measured using the McGill Pain Questionnaire (Short Form). Bars refer to 95% confidence intervals surrounding change in the score at each time point.

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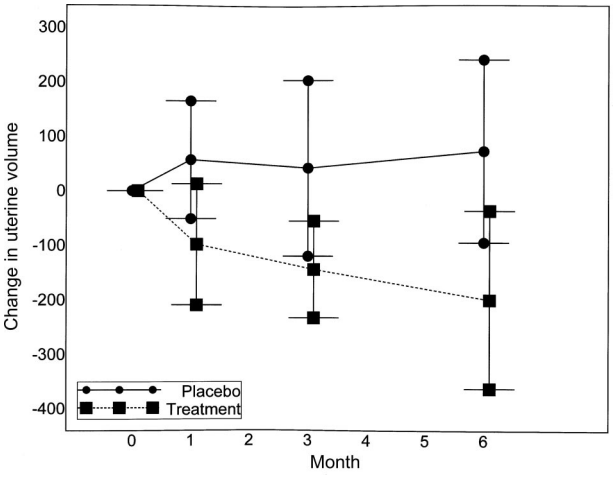

Fig. 5. Change in uterine volumes (mL) among mifepristone and placebo groups. Uterine volumes were measured by vaginal and abdominal ultrasonography. Bars refer to 95% confidence intervals surrounding changes in uterine volume at each time point.

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improvements were seen in the treatment group compared with the placebo group for leiomyoma-specific quality of life ($P<.001$; Fig. 2) and aspects including concern ($P<.001$), activities ($P<.001$), energy and mood ($P=.009$), control ($P=.02$), self-consciousness ($P=.008$), and sexual functioning ($P=.03$). By 6 months, mean Uterine Fibroid Symptoms Quality of Life measures had increased by an average of 50.1 of a possible 100 points (range 0–86), or 135% improvement among treated women, and by 16.7 points (range 14–73) among placebo controls, or a 41% improvement. Symptom severity decreased significantly in both the treatment and placebo groups, but the 6-month scores showed a significantly greater decline among women receiving the treatment (67 to 21) than among women receiving placebo (67 to 50).

Treatment with mifepristone was also associated with improvements in energy and fatigue, health status change, and pain based on SF-36 subscales, but not for physical functioning, physical health, emotional health, emotional well-being, social functioning, or general health. Bleeding decreased markedly among women in the treatment group but not in the placebo group. By the sixth month, 9 of 22 (41%) women in the treatment group had become amenorrheic, compared with none of the women in the placebo group. Mean blood loss index values were significantly lower in the treatment group ($P<.001$; Fig. 3). Treatment had a significant effect on mean hemoglobin levels ($P<.001$); mean hemoglobin levels increased in the treatment group from 12.0 to 13.5 g/dL ($P<.001$) and decreased in the placebo group from 12.2 to 11.6 g/dL ($P=.11$). Anemia, defined as hemoglobin levels below 12.0 g/dL, was present in 11 of 22 (50%) women in the treatment group and in 9 of 20 (45%) women in the placebo group at baseline

(Fisher exact test; $P>.05$). After six months of treatment, 2 of 22 (9%) women in the treatment group and 12 of 20 (60%) women in the control group were anemic (Fisher exact test; $P<.001$).

The treatment group reported decreases in pain as measured by the McGill Pain Questionnaire (Fig. 4), but group differences compared with the placebo group did not reach statistical significance.

Uterine volume (Fig. 5) decreased an average of 200 mL among treatment group women ($P=.02$) and increased an average of 73 mL in the placebo group ($P=.37$). The effect of treatment on mean uterine volume was highly significant ($P<.001$). A secondary regression of uterine volume adjusted for individual baseline volume indicated that uterine volumes decreased an average of 47% in the treatment group and increased an average 10% in the placebo group. Similar and statistically significant differences in reduction in leiomyoma size were noted between groups.

Monthly reports of symptoms including pelvic pain, pelvic pressure, bladder pressure, urinary frequency, low back pain, rectal pain, and pain with intercourse all showed improvements in the treatment group, but not in the placebo group. However, group differences were statistically significant only for pain with intercourse ($P<.05$) and marginally significant for pelvic pressure ($P=.06$).

Potential medication adverse effects were uncommon in both groups. Neither the incidence nor severity of adverse effects, including headache, nausea, vomiting, mood swings, diarrhea, decreased libido, weakness, fatigue, hot flushes, and nervousness, statistically differed between the two groups. Rates of women were higher among the placebo group ($P<.01$). None of the participants showed abnormal liver function during the study. Analgesic use did not differ between groups. No endometrial hyperplasia or other significant endometrial pathology was observed during the study. Higher rates of a characteristic pattern of cystic glandular dilatation were noted among the endometria of treated women. This finding has been previously noted.[11]

At the end of the study, 19 of 20 (95%) women in the treatment group correctly guessed that they had been receiving mifepristone. The remaining woman said she was unsure. Of the 17 women in the placebo group who finished the trial, 9 (53%) correctly guessed they were not receiving the drug, 4 (24%) guessed that they had been receiving the drug, and 4 (24%) said they were unsure. The difference between these two groups in correct guesses is significant (Fisher exact test; $P=.007$). The three placebo and two treatment group women who dropped out did not report on study assignment.

DISCUSSION

A report on evidence-based approaches published by the Agency for Healthcare Research and Quality noted "a remarkable lack of randomized trial data demonstrating the effectiveness of medical therapies" for treatment of uterine leiomyomata.[12] Findings from our study begin to address this void. Using a randomized, double-blinded, placebo-controlled study design, we showed that treatment with mifepristone 5 mg daily for 26 weeks substantially improves leiomyoma-specific related quality of life and bleeding and reduces uterine volume and leiomyoma size among women with symptomatic leiomyomata. Most of the improvement in symptoms and quality of life occurred during the first 8–12 weeks of treatment although reduction in uterine and leiomyoma volume continued to 6 months. Comparable benefits were seen in African-American and white women although power to detect differences by subgroup was limited. Notably, the magnitude of improvement in quality of life (using the same measure) was comparable with that reported in observational studies of uterine artery embolization.[13] No improvements were noted using global measures of pain (McGill Pain Questionnaire) or global physical or mental health status (SF-36) suggesting that benefits of the drug were confined primarily to leiomyoma-specific symptoms.

A post hoc power calculation showed that the final sample size was sufficient to show differences in our primary but not secondary outcomes. A priori power calculations using the planned enrollment of 70 women suggested that the study was powered to detect between-group differences in SF-36 and McGill Pain Questionnaire measures of 0.67 standard deviations or more ($P<.05$.) Post hoc power calculations based on the final sample of 37 women who completed all phases of the trial showed that we had sufficient power to detect differences in group means of 0.93 standard deviations. However, the observed differences in mean placebo and treatment group means for SF-36 and McGill Pain Questionnaire were only 0.46 and 0.53 standard deviations, respectively.

The drug was well tolerated, as evidenced by low dropout rate and absence of appreciable difference in adverse effects between treatment and control groups. In contrast to reports of endometrial hyperplasia noted with 10 mg of the drug,[14] no case of endometrial hyperplasia was noted in this study. These very

promising findings warrant replication through a large multicenter study.

The limitations of our results merit comment. The study sample was small, and recruitment was confined to the Western New York region. Despite intensive efforts, recruitment was less than projected. Nonetheless, the study demonstrated that treatment was associated with significant improvement in leiomyoma-specific quality of life. Moreover, the effects on leiomyoma bleeding and size are consistent with previous studies of the drug.[6,15–18] Although staff and patients were both blinded to study allocation, the dramatic improvements in symptoms including amenorrhea among women in the intervention group resulted in virtually all women in the intervention group suspecting that they received the drug. In contrast, rates of detection were much lower in the placebo group. The extent to which this unmasking biased the results cannot be determined. Although the drug was well tolerated and no serious adverse events were noted, a much larger study sample and longer follow-up period are needed to reliably assess drug safety. A few deaths have been reported after administration of 200–600 mg of mifepristone (and misoprostol) for pregnancy termination; no causal relationship between these deaths and mifepristone has been established.[19]

Further study is needed to determine whether benefits observed over a 6-month treatment period will be sustained with continuation of the drug and whether adverse effects emerge. Previous trials suggest maintenance of symptomatic improvement and reduction in leiomyoma volume up to 1 year.[14] Whether benefits are sustained beyond this time and how quickly symptoms and leiomyoma regrowth recur after cessation of the drug are not known.

In conclusion, treatment of women with symptomatic leiomyomata using low-dose mifepristone for 6 months results in substantial improvements in leiomyoma-specific quality of life, bleeding, and leiomyoma size. Whether these benefits are sustained over longer periods and whether the drug is safe over the long term require further study in larger samples with longer periods of treatment. Completion of such studies will require continued availability of this promising drug.

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